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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416).
12333170/E		
International Application No.	International Filing Date *(day/month/year)*	Priority Date *(day/month/year)*
PCT/AU2003/001212	16 September 2003	16 September 2002

International Patent Classification (IPC) or national classification and IPC

Int. Cl.[7] C12N 5/08, 5/10; A61K 48/00, 35/14

Applicant

THE WALTER AND ELIZA HALL INSTITUTE OF MEDICAL RESEARCH et al

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   [X] This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheet(s).

3. This report contains indications relating to the following items:

   - I [X] Basis of the report
   - II [ ] Priority
   - III [ ] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV [ ] Lack of unity of invention
   - V [X] Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI [ ] Certain documents cited
   - VII [ ] Certain defects in the international application
   - VIII [ ] Certain observations on the international application

Date of submission of the demand	Date of completion of the report
23 January 2004	14 October 2004
Name and mailing address of the IPEA/AU	Authorized Officer
AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	**TERRY MOORE** Telephone No. (02) 6283 2632

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/AU2003/001212

I. **Basis of the report**

1. With regard to the **elements** of the international application:*

☐ the international application as originally filed.

☒ the description, pages **1-31**, as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☒ the claims, pages , as originally filed,
pages , as amended (together with any statement) under Article 19,
pages , filed with the demand,
pages **32-34**, received on **8 October 2004** with the letter of **6 October 2004**

☒ the drawings, pages **1-11**, as originally filed,
pages , filed with the demand,
pages , received on with the letter of

☐ the sequence listing part of the description:
pages , as originally filed
pages , filed with the demand
pages , received on with the letter of

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages

☐ the claims, Nos.

☐ the drawings, sheets/fig.

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report*

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V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1-25	YES
	Claims		NO
Inventive step (IS)	Claims	1-25	YES
	Claims		NO
Industrial applicability (IA)	Claims	1-25	YES
	Claims		NO

2. Citations and explanations (Rule 70.7)

The specification discloses a method of treating diabetes comprising isolating haematopoietic stem cells from a patient, introducing a genetic construct expressing proinsulin into these cells and then re-introducing the cells back into the patient. The method produces tolerance to pro-insulin in the patient. Although the examples do not provide explicit disclosure of this method: the examples only recite use of stem cells expressing pro-insulin wherein the stem cells are obtained from transgenic mice, rather than use of stem cells isolated from non-transgenic mice and transfected with proinsulin *ex vivo*, it is considered that there is sufficient understanding and application of the *ex vivo* transfection steps in the art to support the method of the claims.

D1 J Clin Invest (2003) 111(9), 1357-63
D2 Trends Immunol (2003 Apr) 24(4), 176-80
D3 J Immunol (2002) 168, 1103-1112
D4 WO 2001 025398 A2 (BIOTRANSPLANT INC) 12 April 2001
D5 J Neuroimmunol (2000) 103(1), 51-62
D6 Proc Natl Acad Sci USA (2002) 99(1), 351-9

New Citation
D7 Life Sciences (1999) 65(20), 2041-7

Novelty and Inventive Step

D1 and D2 were published after the priority date of the present application and thus are not relevant to the novelty or inventive step of the claims.

D3 discloses the adoptive transfer of stimulated anergic T cells from transgenic mice expressing the nuclear autoantigen OVA into naïve mice. The naïve mice then demonstrate tolerance to the OVA nuclear autoantigen. Although the citation also mentions exploring whether or not this principle will work with non-nuclear autoantigens, it does not provide any clear suggestions or prediction that it will. It also does not direct the PSA toward secreted autoantigens such as proinsulin. As such, although the citation discloses preliminary work in an area related to the applicant's invention, it does not provide sufficient direction to suggest to the PSA that the subject matter of the claims could be achieved as a matter of routine. Therefore, the citation is not clearly relevant to the novelty or inventive step of the claims.

Continued in supplemental box.

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Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of Box V2 (Novelty and Inventive Step)

Similarly, D4 discloses methods of introducing cells expressing neoantigens into a host to induce tolerance to the neoantigens. The methods are intended to reduce adverse reactions to neoantigens that may be administered in association with therapeutic compositions, for examples vectors that may be used to introduce gene therapy compounds or non-therapeutic epitopes on therapeutic antibodies. Although these methods introduce the concept of inducing tolerance by *ex vivo* transduction and then re-introduction of a patients own cells to induce tolerance, the citation is using this method for a different purpose and there is no suggestion that the same method could be used to induce tolerance to autoantigens or to treat autoimmune disease such as diabetes. Therefore, the citation does not clearly challenge the novelty or inventive step of the claims.

D5 discloses gene transfer of the autoantigen MBP into mouse bone marrow derived stem cells. However, this method is directed at understanding the mechanisms that operate in autoimmunity and is not directed at developing methods of treating autoimmune diseases such as IDDM. Therefore the citation does not deprive the claims of novelty or an inventive step.

D6 is a general discussion of the importance of antigen presenting cells, in particular dendritic cells in tolerance. The citation does not direct toward the methods of the claims or mechanisms specifically directed at inducing tolerance to insulin. As such the citation does not deprive the claims of novelty or an inventive step.

D7 discloses a method of introducing genetic material encoding proinsulin into haematopoietic stem cells. However the citation does not expand on this method to suggest its application to treating IDDM. As such the citation does not clearly impact on the novelty or inventive step of the claims.

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